Radical Synthetic Strategies for Medicinal Chemistry

Research Thesis

Presented in partial fulfillment of the requirements for graduation

with research distinction in Chemistry in the College of Arts and Sciences of The Ohio State University

by

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April 2018

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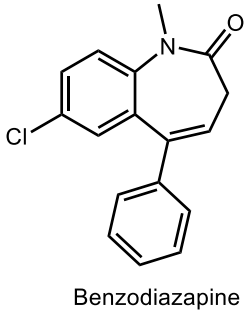
Abstract:

Synthetic chemistry plays a key role in drug discovery. Finding a simple method to prepare drug candidates is the important to synthetic chemists. However, approaching drug molecules by traditional methods needs several steps which give a low yielding and time-consuming process. To rapidly approach target drug molecule, chemists now use C-H functionalization as a powerful tool to modify small molecules. Radical mediated C-H functionalization is currently a hot topic in synthetic chemistry due to its mild and highly selective properties. Besides C-H activation, radical mediated C-O activation also allow scientists to modify drug cores which cannot be reached previously. Herein, I report three related projects I joined during the two-year undergraduate researches in Nagib lab. The first one is polarity-reversal cascade for C-H functionalization of heteroarenes. In this project, quinoline and its derivatives are functionalized via a umpolung strategy. During the summer, to approach the cheap and effective catalyst, I tried to accomplish coupling reaction between olefins and aldehydes by photo-induced iron catalyst. The last one is silver-catalyzed decarboxylative fluorination of alcohol. An additive-based robustness screening is done to check the functional group compatibility in this project.

General Introduction

Every year there are many new drugs being invented and to be approved by FDA. In 2017, totally 44 types of novel drug were approved by FDA and already 9 drugs were approved in 2018 till now[1,2]. Organic chemistry is considered as one of the main drivers in drug discovery process[3]. New techniques developed help synthetic chemists and medicinal chemists to better utilize organic chemistry for synthesis[3]. Normally drug molecules are complex and needs synthetic chemists to find a way to synthesize. In traditional method, to synthesize a complex molecule, multiple steps are required, including addition of other functional group precursor and protection of functional group, which are usually troublesome and cause the low yielding. For example, paclitaxel total synthesis by Norton group was a 46-steps procedure and the overall yield was very low[4]. These limitations cause the high cost to pharmaceutical company and then influence the final price of these medicines that people cannot afford. Nowadays, with the development of organic chemistry in specific areas, this limitation is going to be broken.



Benzodiazapine

Figure 1: Benzodiazapine, a common drug molecule which needs several steps to synthesize

Radical chemistry has been developed for a long time. The most well-known one is halogenation of alkanes under light condition. Different from common thoughts, radicals are usually mild and highly selective. To generate a radical, there are several methods, including generation and homolysis of a weak bond and photocatalysis.

The stability of a radical depends on its electronegativity and position. Oxygen-center radical and nitrogen-center radical are generally unstable due to their high electronegativity[5]. Harnessing these less stable radicals, more stable radicals can be prepared. A less stable radical can be generated via forming and homolyzing a weak bond[5]. In Hofmann-Löffler-Freytag reaction, a weak N-Cl bond is formed and homolyze under light or heat condition[5]. This unstable radical can abstract hydrogen atom in specific position, usually 1,5-hydrogen atom transfer or 1,5-HAT because of the stable 6-member ring intermediate, to generate a more stable carbon center radical. Then this new radical can trap other radicals or trapped by radical traps to access the target products.

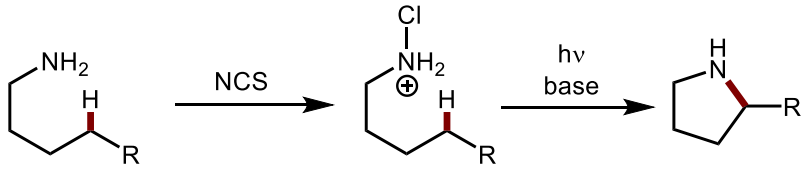


Figure 2: Hofmann-Löffler-Freytag Reaction[5]

Besides generating a weak bond, metal catalysts can also join to radical generation by oxidizing or reducing bonds via single electron transfer (SET). Excited by irradiation, some photocatalysts, like $Ir(ppy)_3$ and $Ru(bpy)_3$, enter excited state and become triplet state via metal to ligand charge transfer (MLCT) and rapid intersystem crossing (ISC)[6]. Then photocatalysts have both oxidant and reductant potential for redox reaction based on the situation[6]. Due to the reactivity of radicals, they can also join the C-H functionalization which is a hot topic in synthetic chemistry now.

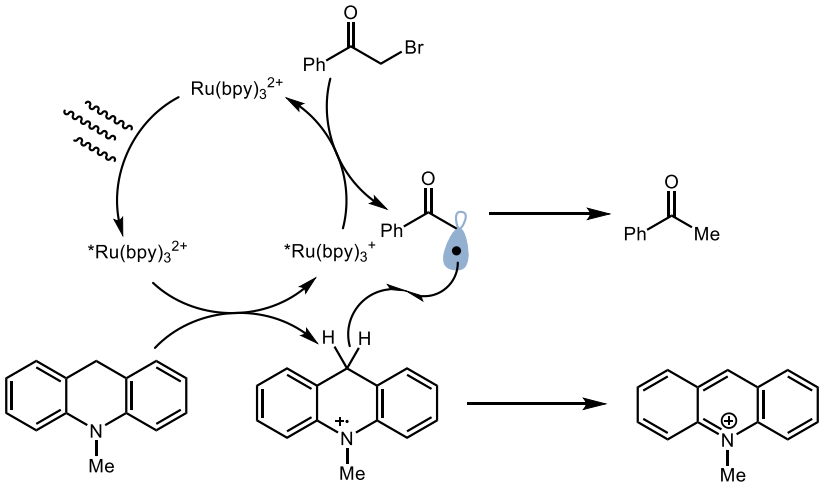


Figure 3: Photo-induced dehalogenation via radical pathway[6]

C-H bond usually is considered as a strong bond due to the high dissociation energy, which is around 105 kcal/mol[7]. The traditional methods in organic chemistry usually cannot overcome the energy barrier to directly activate this strong bond. In 1955, Shunshuke Murahashi reported a cobalt-catalyzed synthesis of phthalimidines, which was considered as very early reported C-H activation[8]. After this report, more methods for C-H functionalization were developed, including using metal catalyst, like iridium and rhodium, and other methods.

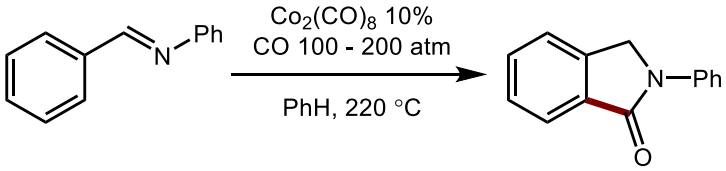


Figure 4: Cobalt-catalyzed C-H Functionalization by Shunshuke Murahashi[8]

Has been developed and completed for several years, C-H functionalization now is a hot topic in synthetic chemistry, which is also called as Holy Grail of organic synthesis[9]. Many synthetic groups are doing C-H activation in different methods. Metal catalysts, like palladium, are broadly used in C-H activation by forming a metal complex intermediate with ligands. Ligands also play an important role in metal-catalyzed C-H activation. To activating C-H bond for asymmetric catalysis, the ligand should be designed as chiral. With the help of various ligands and metal catalysts, more C-H activation can be achieved with enantio- and chemo-selectivity.

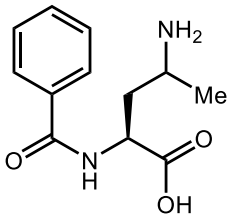


Figure 5: Ligand for asymmetrical catalysis by Yu group[10]

Radical chemistry, as a major role in organic chemistry, shows its importance with more new reactions being developed and published. By combining radical chemistry and metal catalysis, C-H functionalization is also not as hard as previously. Synthetic chemistry improves the medicinal chemistry process and only harness all synthetic methods, more drug candidates will be discovered.

Herein, three projects I joined during the two-year undergraduate researches in Nagib lab, related to radical chemistry, medicinal chemistry and C-H/C-O activation, are reported.

Projects:

a. Polarity-Reversal Cascade for C-H functionalization of Heteroarenes

In medicinal chemistry, heterocycles are usually key backbones for discovering new drug candidates[11]. In 2010, more than 80% of top small molecule drugs have at least one heterocycles[11]. Acting as bioisosteres for many drug candidates, heterocycles with a variety of spatial structure and physicochemical properties provides a large scope for optimization of drug candidates[11]. Hydrogen bonding, lipophilicity, polarity and other factors give heterocycles a key role in design of pharmaceutical molecules[11].

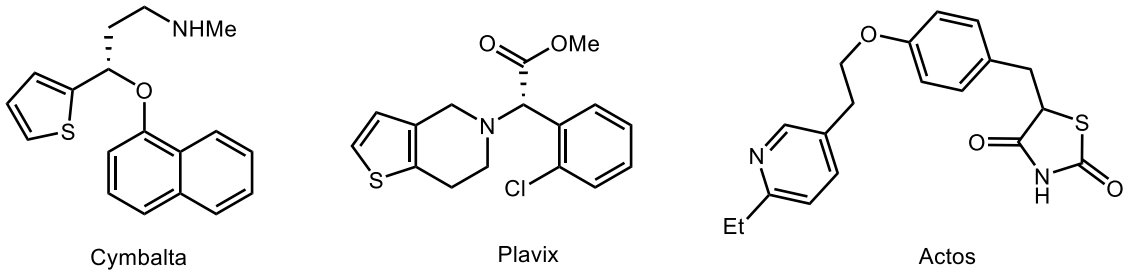


Figure 6: Drug Containing Heterocycles[11]

Quinoline, as a commercial available heteroarene, exists in many drug molecules, including Quinine the most famous anti-malarial drug[12]. Besides Quinine, chloroquine, pamaquine and quinacrine etc. are all good anti-malarial drug containing quinoline[12]. Other quinoline containing drugs have broad effects, including anti-inflammatory, antibacterial antiviral effects[13]. Due to the wild usage in medicinal chemistry and commercial accessibility, functionalizing quinoline can allow medicinal chemists to find more potential drug molecules.

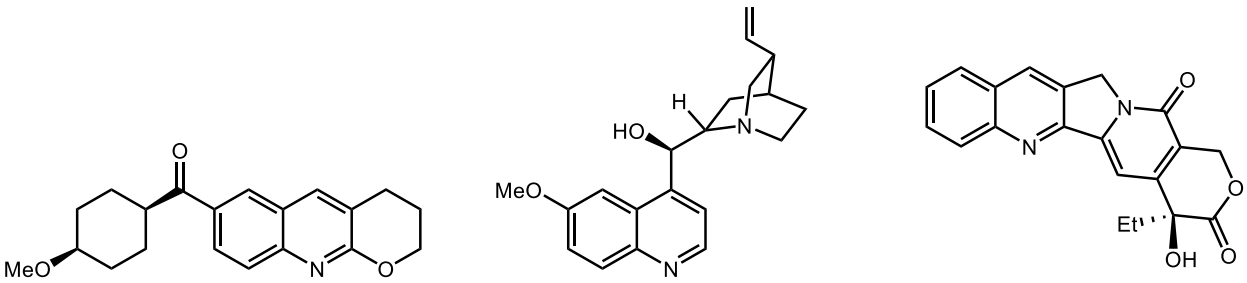


Figure 7: Drug Molecules Containing Quinoline Core

Minisci reported a reaction in 1971 (Figure 8), which allow chemist to functionalize quinoline. Under acid condition, 2-methylquinoline is protonation and more electron-deficient[14]. Methanol is oxidized to generate an α-oxy radical, which is nucleophilic due to the electron-donating conjugation effect of oxygen[14]. Then this radical couples with protonated quinoline in

position 2, which is more electron-deficient position[14]. Following the deprotonation and oxidation steps, the target molecule is generated[14].

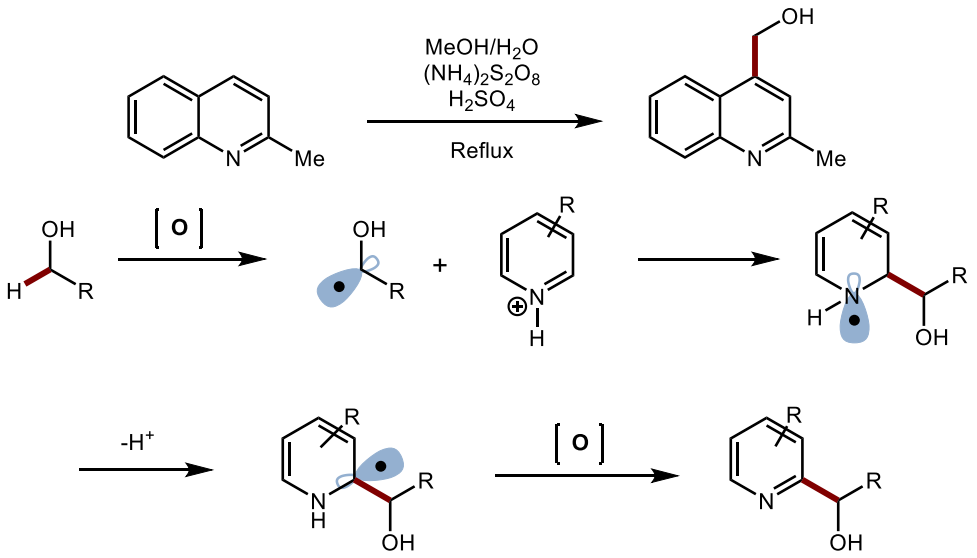


Figure 8: Minisci Reaction and Proposed Mechanism[14]

Minisci reaction allows chemist to rapid access the quinoline core to discover the more drug candidates. However, due to the electron and polarity properties, protonated quinoline can only accept nucleophilic radicals but not electrophilic radicals, which are not polarity matches. By working with Jeremy Lear and Quentin Buquoi, we reported a three-component Minisci reaction which uses polarity-reversal strategy to allow us to access electrophilic radical in quinoline core.

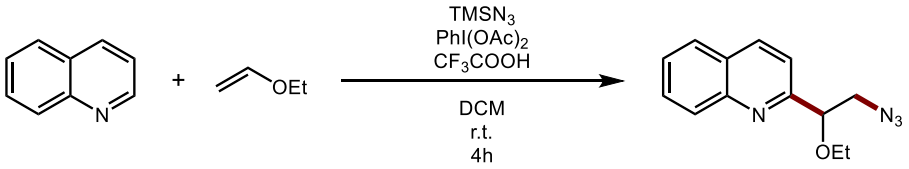


Figure 9: Three-component Minisci Reaction

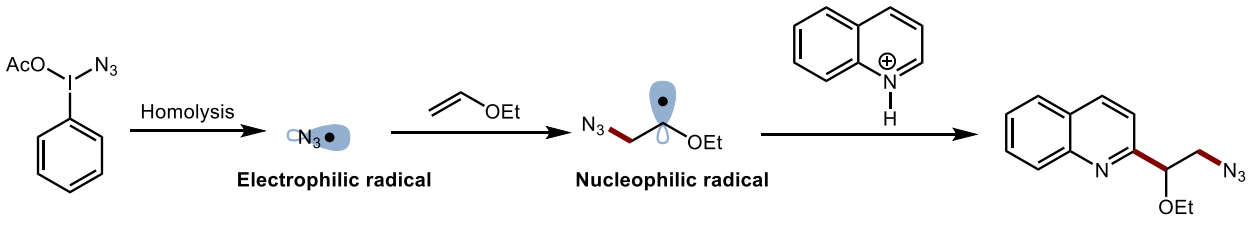


Figure 10: Proposed Mechanism of the Reaction

(Diacetoxyiodo)benzene (PIDA) reacts with trimethyl azide ($TMSN_3$) to generate a weak I-N3 bond, which the dissociation energy is around 38 kcal/mol[7]. I-N bond then homolyze and an azide radical is generated. Ethyl vinyl ether, as a strong radical trap, then rapidly traps azide

radical to generate a new radical. Azide radical is an electrophilic radical while the new generated radical is a nucleophilic radical, because of the conjugation effect of oxygen, and during this procedure, the polarity of the radical is reversed.

Polymerization happens in this reaction as a side reaction. To minimize this side reaction, we used multi-addition method, in which $TMSN_3$, PIDA and ethyl vinyl ether are added in several times to ensure the new generated radicals could couple with protonated quinoline immediately.

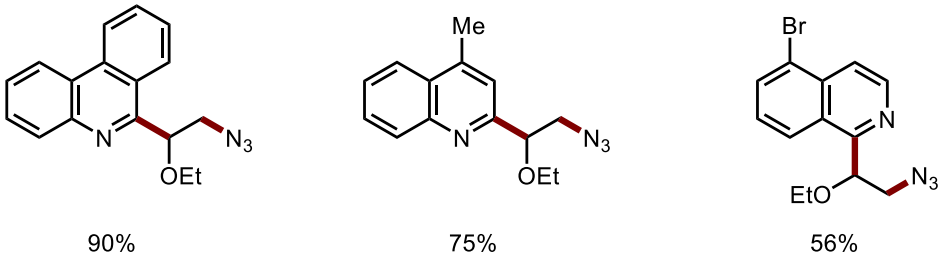


Figure 11: Partial Substrate Table

The substrate table for the reaction includes several quinoline derivatives which show the strong functional group compatibility and could have potentials in discovering more drug candidates. Three substrates were characterized by me, and the yields were up to 90%. Also, these substrates include quinoline and isoquinoline core to prove that this method can also be applied in other heteroarenes.

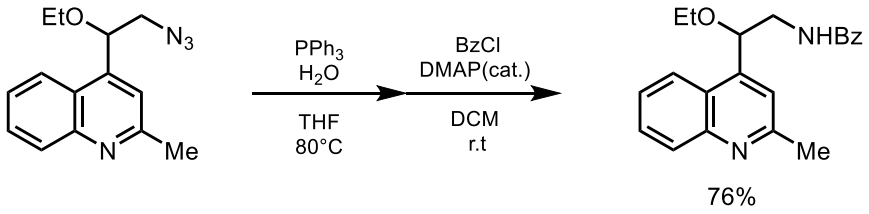


Figure 12: Post-functionalization of Product

Also, to further approach the drug candidates, post-functionalization is tested. Reacting with triphenylphosphine and water, the azide group is reduced to amine group by Staudinger reaction, then the product react benzoyl chloride catalyzed by DMAP to approach amide group, which is also an important functional group in medicinal chemistry.

In step 1, triphenylphosphine attacks the azide group to from a N-P bond, with a positive charge on phosphine atom. Then N with negative charge attacks P to form a four-member ring intermediate. Nitrogen gas then leaves and a new N=P bond forms following the addition of water and release of triphenylphosphine oxide to form the amine product.

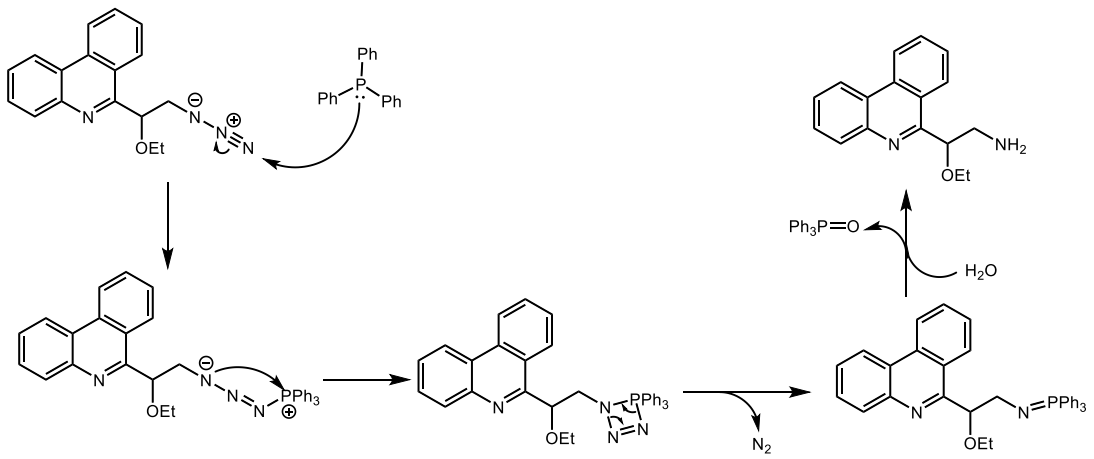


Figure 13: Mechanism for Step 1

Herein, we reported a novel three-component Minisci reaction with polarity-reversal strategy to allow us to utilize electrophilic radical to functionalize quinoline core; also, post-functionalization reaction also prove that the further reaction in drug discovery.

b. Iron-Catalyzed Coupling Reaction with Aldehyde and Olefin

Metal-catalyzed cross coupling reactions are commonly used in organic synthesis. Suzuki-Miyaura coupling and Buchwald-Hartwig amination are the most commonly used in medicinal chemistry to construct C-C and C-N bonds while other coupling reactions are also used[15]. However, for these reactions, the metal catalysts are normally palladium, or other expensive metals, which restrict their usage due to the high price. Discovering cheap and effective metal catalyst then becomes a hot topic for synthetic chemists.

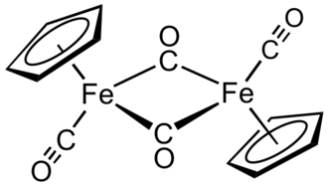


Figure 14: η^5-cyclopentadienyliron dicarbonyl dimer

Iron is a cheap metal and its applications in coupling reactions, in which iron catalysts are used to construct C-C bond and C-heteroatom bonds, has been wildly reported[16]. η^5-cyclopentadienyliron dicarbonyl anion, or Fp anion, is a strong nucleophile[17]. Due to its unique properties, Fp anion is used to do the substitution reactions, including Fe-C bond formation and Fe-metal bond formation[17]. Also, addition reactions of Fp anion with electrophiles are also reported[17].

Anion	Relative nucleophilicity
$CpFe(CO)_2^-$	70,000,000
$CpRu(CO)_2^-$	7,500,000
$CpNi(CO)^-$	5,500,000
$Re(CO)_5^-$	25,000
$CpW(CO)_3^-$	500
$Mn(CO)_5^-$	77
$CpMo(CO)_3^-$	67
$CpCr(CO)_3^-$	4
$Co(CO)_4^-$	1

Table 1: Reactivity of Metalates with Organohalides[17]

Mankad group reported a palladium-free heck coupling between benzyl chloride and styrene by Fp anion under photochemical condition in 2014[18]. The proposed mechanism is shown as a photoinduced alkene-insertion pathway[18]. Based on their report, a C-Fe bond forms during the reaction, following CO dissociation under UV condition and alkene insertion[18]. NaO^{t}Bu then does elimination to complete the catalyst cycle[18].

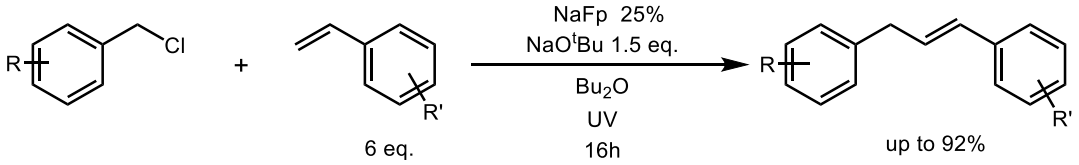


Figure 15: Reported Reaction by Mankad Group

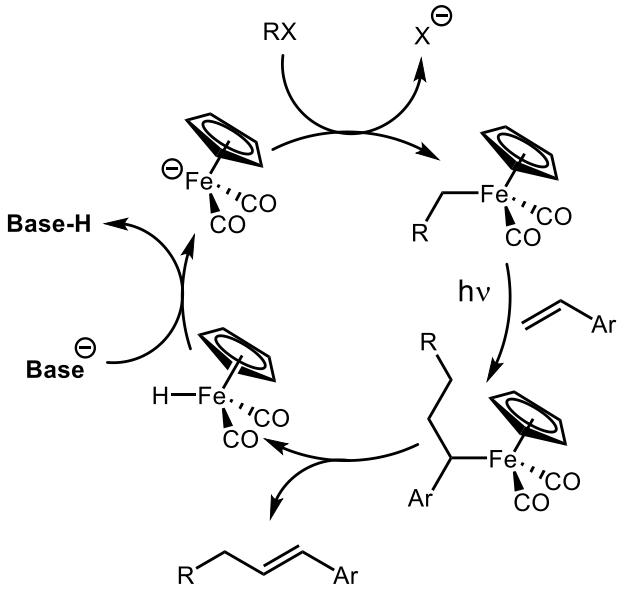


Figure 16: Proposed Mechanism Reported by Mankad Group[18]

Based on the discovery of Mankad group, we proposed that Fp anion could also be used in other coupling reactions. Aldehydes are important series of chemicals that are wildly used in industrial and pharmaceutical area. Carbonyl groups have advanced reactivity due to the polarity difference between carbon and oxygen, in which carbon in carbonyl group shows electrophilic while the oxygen shows nucleophilic. However, forming a C-C bond between aldehyde and an electron deficient molecule is hard due to the polarity mismatch. Umpolung strategy is used in this condition; benzoin condensation and Cannizzaro reaction are two well-known reactions based on this strategy. By increasing the acidity of the hydrogen on carbonyl group, a carbon-center anion is generated and then it can attack the electron deficient carbon to construct a C-C bond between two electron-deficient carbon. We proposed if Fp anion can be used to do the coupling reaction between aldehyde and olefin with umpolung strategy.

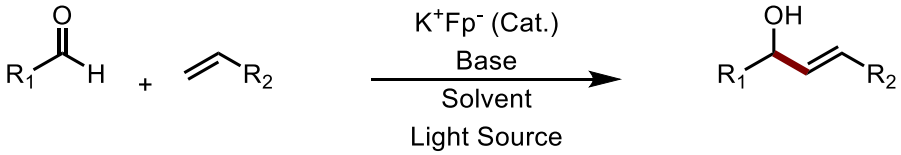


Figure 17: Proposed Reaction

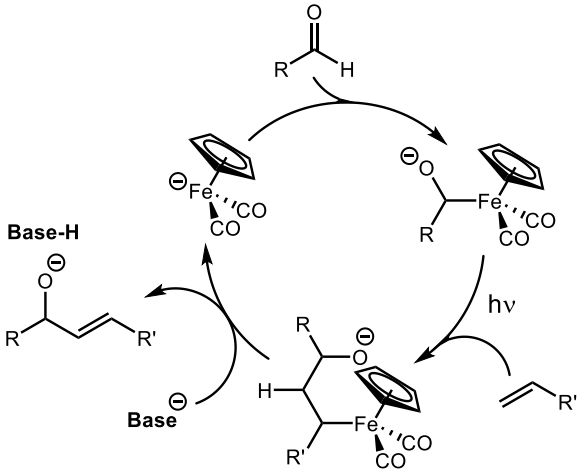


Figure 18: Proposed Mechanism

The proposed mechanism is shown in figure 18. Fp anion, acting as a strong nucleophile, attacks aldehyde to form a metal complex. Under light condition, CO dissociation and alkene insertion happen based on the report from Mankad group. The product is generated and Fp anion is reproduced by basic elimination.

Starting from reproducing Mankad's reaction condition, however, I couldn't repeat the reaction with reported yield. In Mankad's report, the reaction goes through a silica plug following sequence wash with diethyl ether[18]. However, Fp anion could not be removed in my situation so the NMR spectra for reactions were disturbed. Then by pre-addition of silica in reaction and washing with hexane, remaining Fp salt was mostly removed and the internal

standard, mesitylene, was used to measure the NMR yield of the reaction. However, the repeated reactions could not reach the yield as high as reported yield.

The project was then moved on. Each step of the reaction should be proved separately. The addition of Fp anion to aldehyde, which was proposed as the first step, was proved by quenching the reaction with acid to break C-Fe bond, following the purification with silica plug and the NMR technique. However, the next step, which should be the C-C bond formation, didn't work when I used the same condition as Mankad group reported, so I started the optimization step.

Several solvents, including dichloromethane, tetrahydrofuran, diethyl ether and toluene, were degassed by freeze pump thaw and used as solvent. However, no product was observed when I used different solvents. Different aldehydes were also screened. However, due to the side reaction between strong base and aldehyde with α-hydrogen, aldehydes without α-hydrogen were accessible for the reaction but still no target molecule was observed.

Then I assumed the olefin might play the key role in the reaction since alkene insertion is required for further C-C bond formation. I then used 2-propenenitrile since it is more electron-deficient and might be better in alkene insertion step. When 2-propenenitrile was used as the olefin substrate, 2-(benzyloxy)acetonitrile was isolated due to the strong nucleophilicity of new generated alkoxide intermediate. Acyl chloride then was used in reaction to block the alkoxide region to prevent the further side reactions. However, the target molecule was still not observed.

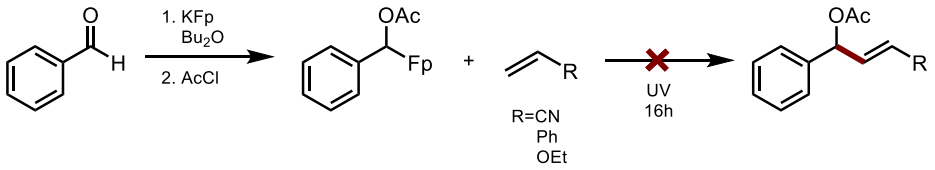


Figure 19: New Strategy to Block Alkoxide and Use of New Olefins

Also, I supposed the accessibility of aldehyde and tried to use different substrates to replace aldehydes. Benzoyl chloride and 2-bromoacetophenone were used to test the reaction. Constructing a C_{sp2} and C_{sp3}.

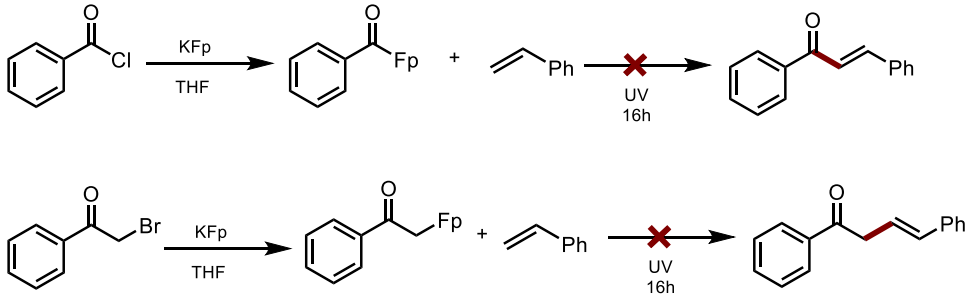


Figure 20: Other Substrates for Proposed reaction

Due to the inaccessibility of the tests, this project is temporary paused, and I move to the other reactions.

c. Silver-Catalyzed Decarboxylative Fluorination of Alcohol

Fluorine chemistry is a broad area and plays a dramatic role in medicinal chemistry. During the drug design, equipping with fluorine could change the properties of the drug molecule[19]. Due to the high polarity of fluorine, the pka of a molecule can be dramatically changed when equipped with a fluorine; also, fluorine-containing drug molecules have very different logP value, which represent the solubility ratio between organic phase and aqueous phase, to target different active sites[20]. The 18F isotope can also be used as biological probe which is applied to study the structure in human body[19].

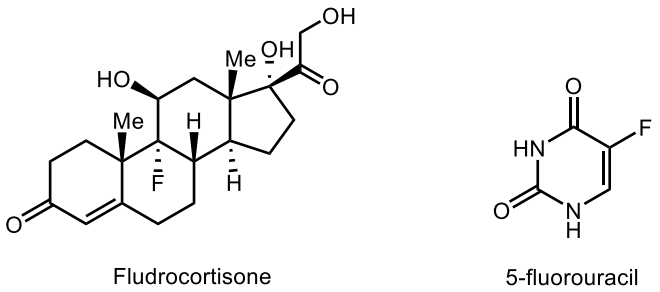


Figure 21: Some Fluorine-Containing Drug Molecule[19]

However, fluorination of organic molecules is usually tough since strong and dangerous fluorine sources are used, including F_2 and HF[21]. To find a mild method to construct C-F bond is also the target for synthetic chemists.

Alcohols are very common chemicals and most of them are commercial available and cheap. Several groups reported their discovery of fluorination of alcohols. However, most of these methods require fluoride as the fluorine source, including DAST or PyFlour, which are usually hard to handle or very sensitive[22,23].

By working with Dr. Zuxiao Zhang, we reported a novel and mild way to do the fluorination of alcohol by silver catalyst. Then the robustness screening was tested to check the compatibility of reaction with other functional groups.

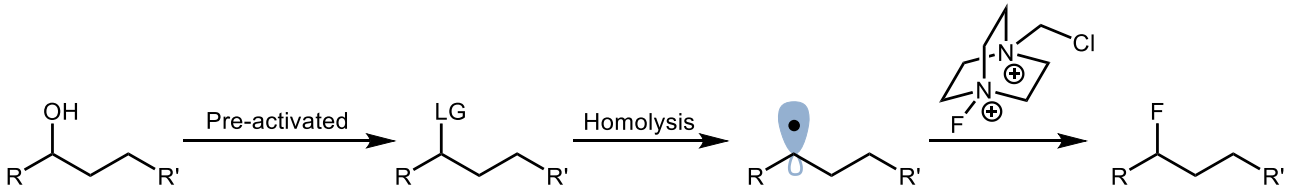


Figure 22: Reaction strategy of Fluorination

Alcohols are pre-activated before the reaction. The pre-activation step is easy to handle and gives quantitative yield. Selectfluor was screened as the best fluorine cation source, while

acetonitrile and 50 ℃ were found as the best solvent and reaction temperature. The substrate scope was broad and the yield of the standard reaction (Figure 23) could be up to 83%.

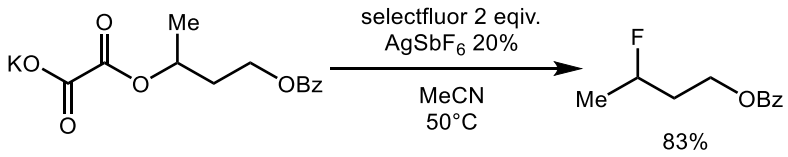


Figure 23: Standard Reaction of Fluorination

The mechanism for the reaction is still not clear. Li group reported a possible mechanism in their decarboxylative fluorination[24]. Silver (I) is oxidized by SelectFluor to form a Ag-F bond and Ag (I) is oxidized to Ag (III). Ag (III) oxidizes substrate and is reduced to Ag (II) while a radical is generated via decarboxylation twice. Then the radical traps fluorine to form the final product while Ag (II) is reduced to Ag (I)

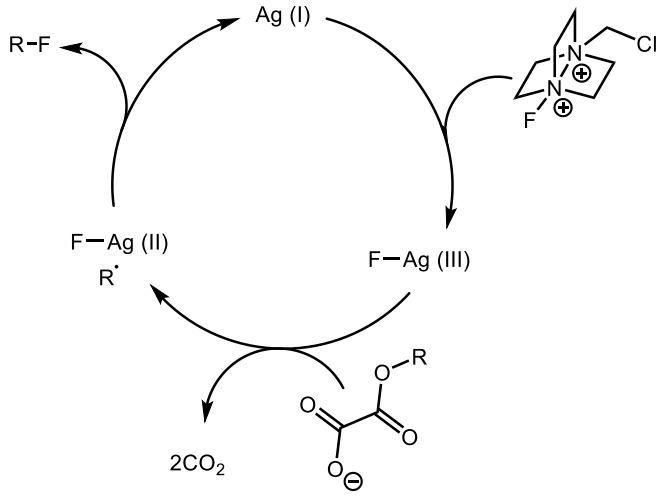


Figure 24: Possible Mechanism

To prove the reactivity to be unique and novel, methods reported by other groups were used with our substrate[24,25,26]. The yields were reported as NMR yield with CF_3DMAc as the internal standard. Ir[dF(CF_3) ppy]$_2$(dtbbpy)PF_6 was used as Ir photocatalyst based on reported method. Acetone and acetone/water 50:50 were both used for the method from Li group. The acid form and the salt form of the substrates were both used based on the report from Hartwig group. Based on the NMR yield, reaction with methods from MacMillan group and Li group gave lower yield while method from Hartwig group gave trace yield. These tests prove the uniqueness and novelty of our reaction.

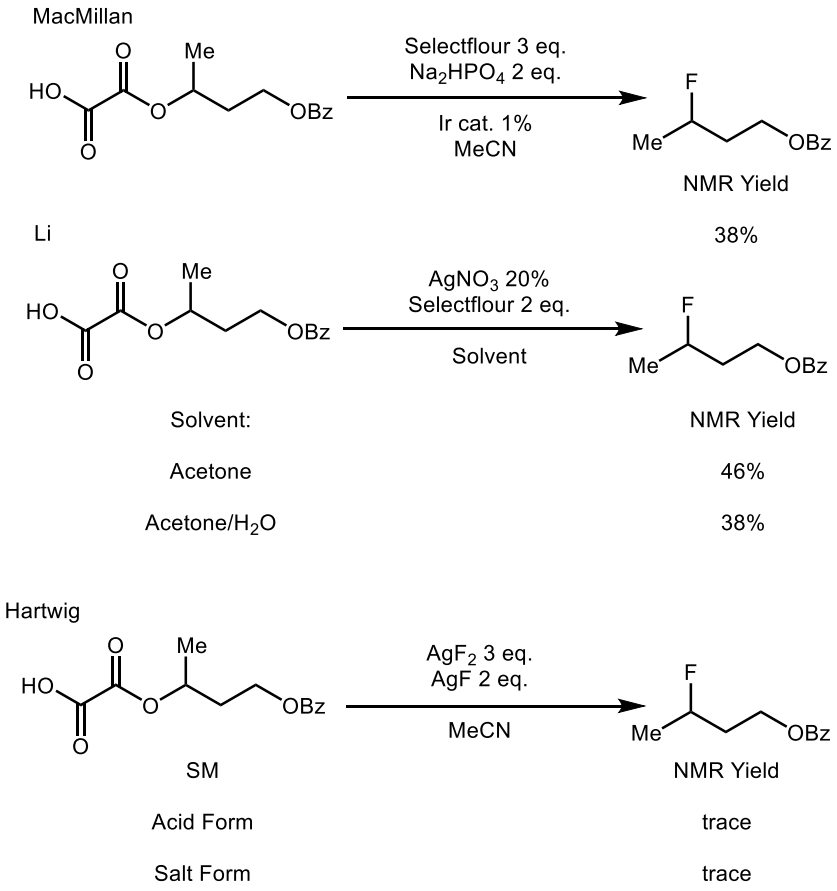
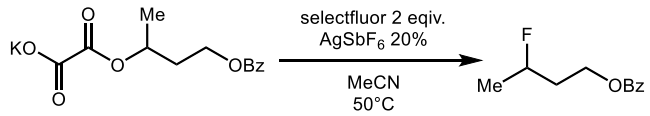


Figure 25: Methods from Other Groups with Standard Substrate

Due to the importance of fluorination in medicinal chemistry, the compatibility of the reaction condition with functional groups and heterocycles should be high enough to prevent decomposition of drug molecules and other side reactions when this method is applied to discover more potential drug candidates. Additive-based robustness screening was applied for this target. Totally 18 different additives, including simple molecules and complex molecules with various functional groups and heterocycles, were added during the reaction preparation procedure. For each reaction, the product yield was NMR yield with CF_3-DMAC as the internal standard, and the remaining amount of additive was measured by GC with mesitylene as internal standard. A calibration curve for each additive was generated by preparing three solutions of additive in different amount (0.04 mmol, 0.1 mmol and 0.2 mmol) with same amount of mesitylene (0.2 mmol) as internal standard. The ratio of integration area for standard to that for additive was calculated and then the calibration curve was generated, in which the amount of additive as x-axis and the ratio as y-axis.



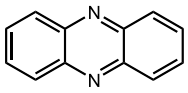
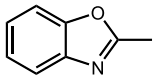
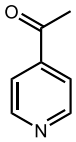
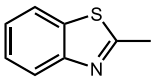
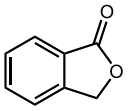
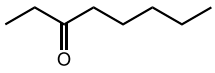
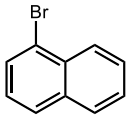
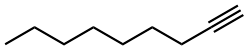
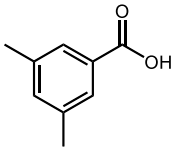
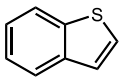
	Yield	Additive Remaining		Yield	Additive Remaining
	12%	64%		83%	38%
	59%	78%		78%	33%
	74%	18%		92%	96%
	86%	62%		77%	27%
	64%	trace		65%	61%
	trace	trace			

Table 2: Robustness Screening Results

From the table, the compatibility of the reaction with other functional groups are shown. Through comparing the NMR yields of these reactions with standard reaction. Based on the table, most of additives are compatible with the standard reaction condition to give similar yields. Reaction with phthalide gave a higher yield than standard condition, implying phthalide may be good for the reaction. Reactions with phenazine, estrone, thianaphthene and salicylic acid gave very low yields, which means the reaction is not compatible with these molecules and other derivatives. In conclusion, this reaction condition reveals high functional groups and heterocycles tolerance.

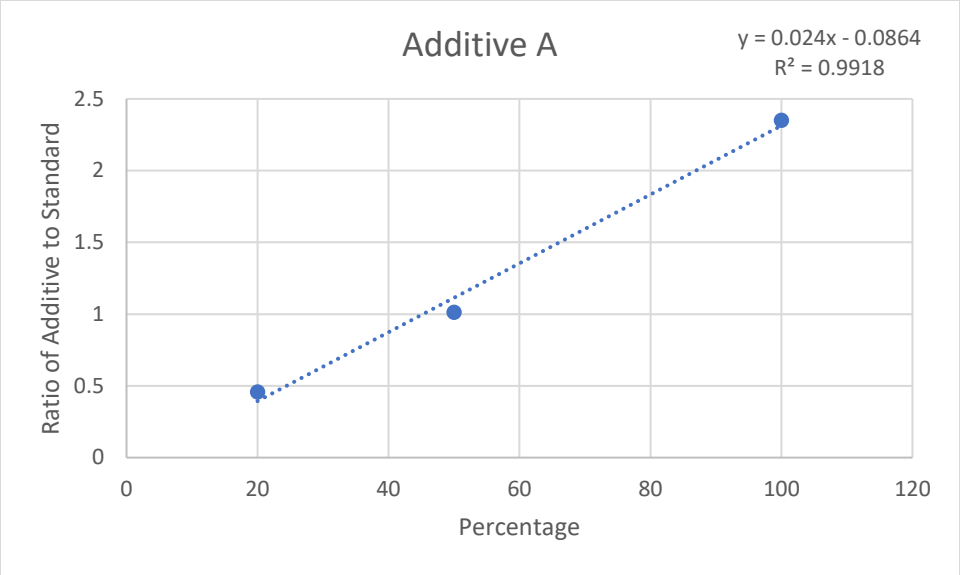


Figure 26: Calibration Curve for Additive A

Also, the amounts of remaining additives were measured via GC or NMR. For some compounds, the GC method was used to determine the additive remaining with a calibration curve generated with different amount of additive and same amount of internal standard. 0.04 mmol, 0.1 mmol and 0.2 mmol of additives were used and 0.2 mmol of internal standard were used. The trend of the ratio between additive and standard with percentage of additive will be a line and then the ratio from sample could be used to determine the remaining additives. Generally, heterocyclic compounds and some functional groups are compatible with the reaction condition, with minimum amount of them are consumed, showing the good potential of the reaction in fluorination of known drug molecules and drug candidates.

In this project, we reported a mild and convenient method of fluorination of alcohols, which is catalyzed by silver. Robustness screening is also done to check the functional group compatibility with standard condition of reaction, and the results showed high functional group and heterocycle tolerance.

Conclusion

In the two-year lab experience, I did three projects. In the first project, polarity-reversal cascade for C-H functionalization of heteroarenes, I characterized three substrates and did the post-functionalization of one product to further approach the drug candidates. In the second project, I used η^5-cyclopentadienyliron dicarbonyl anion, or Fp anion, to do the coupling reaction between aldehyde and olefin under photochemical condition and proved that this method was not very accessible and need more modification in the future. Robustness screening was done in the last project, silver-catalyzed decarboxylative fluorination of alcohol, to prove the compatibility of the reaction with other functional groups.

Acknowledgement:

I thank Prof. David A. Nagib and all Nagib lab members, especially Jeremy Lear, Quentin Buquoi and Dr. Zuxiao Zhang for the guide and assistance. Thank to Department of Chemistry and Biochemistry for giving me a chance to have undergraduate research experience and offering me Kraska Endowed Chemistry Scholarship Fund. Also thank to Undergraduate Research Office for Mayers Summer Research Scholarship.

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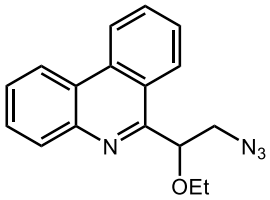
Supporting Information:

6-(2-azido-1-ethoxyethyl)phenanthridine

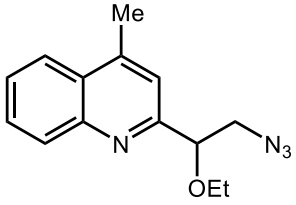


Colorless liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (q, J=14.8 Hz, 2H), 8.59 (dd, J = 4.5, 1.6 Hz, 1H), 8.20 (m, 1H), 7.88 (ddd, 1H), 7.77 – 7.67 (m,3), 5.37 (dd, J=4.5, 12.8 Hz, 1H), 4.07 (dd, J=13, 8.6 Hz, 1H), 3.66-3.61 (m, 3H), 1.25 (t, J=7 Hz, 3H).

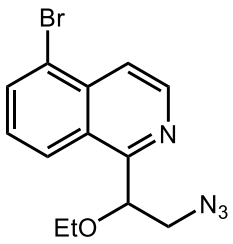
^{13}C NMR (151 MHz, $CDCl_3$) δ 157.4 (s), 143.2 (s), 133.4(s), 130.7 (s), 130.3 (s), 128.8 (s), 127.4 (s), 126.1 (s), 124.7 (s), 124.1 (s), 122.6 (s), 122.0 (s), 83.0 (s), 77.2 (s), 65.2 (s), 53.9 (s), 15.4 (s).

2-(2-azido-1-ethoxyethyl)-4-methylquinoline



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (ddd, J = 18.9, 8.4, 0.8 Hz, 2H), 7.71 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.61 – 7.52 (m, 1H), 7.47 (d, J = 0.7 Hz, 1H), 4.77 (dd, J = 7.8, 3.5 Hz, 1H), 3.65 – 3.57 (m, 3H), 2.75 (d, J = 0.9 Hz, 2H), 1.34 – 1.27 (m, 3H), 1.27 – 1.15 (m, 2H).

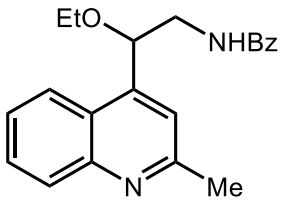
1-(2-azido-1-ethoxyethyl)-5-bromoisoquinoline



Colorless liquid

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.91 (s), 143.21 (s), 135.89 (s), 134.03 (s), 127.97 (s), 127.76 (s), 124.61 (s), 122.51 (s), 120.10 (s),82.31 (s), 77.22 (s), 65.34 (s), 54.27 (s).

N-(2-ethoxy-2-(2-methylquinolin-4-yl)ethyl)benzamide

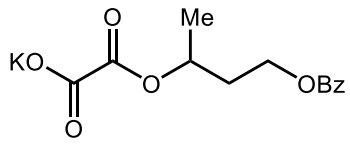


White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J=7.7 Hz, 1H), 8.07 (dd, J=8.4, 0.7 Hz, 1H), 7.84 – 7.77 (m, 2H), 7.71 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.62 – 7.40 (m, 5H), 6.70 (s, 1H) 5.29 (dd, J = 8.5, 3.7 Hz, 1H), 4.26 – 4.09 (m, 1H), 3.88 – 3.77 (m, 1H), 3.88 – 3.40 (m, 1H), 3.31 (ddd, J = 13.9, 9.2, 4.4 Hz, 1H), 2.77 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.77 (s), 158.81 (s), 148.26 (s), 145.35 (s), 134.33 (s), 131.71 (s), 129.46 (s), 129.41 (s), 128.71 (s), 126.93 (s), 126.22 (s), 124.60 (s), 123.13 (s), 118.79 (s), 77.22 (s), 77.16 (s), 65.45 (s), 45.90 (s), 25.55 (s), 15.42 (s).

Potassium 2-((4-(benzoyloxy)butan-2-yl)oxy)-2-oxoacetate



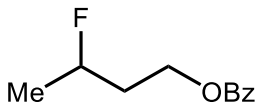
White solid, m.p = 163.1-164.4℃

^{1}H NMR (600 MHz, DMSO) δ 8.00 – 7.94 (m, 2H), 7.66 (tq, J = 4.5, 1.6 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 5.02 – 4.86 (m, 1H), 4.35 – 4.29 (m, 1H), 4.23 (dt, J = 11.1, 6.8 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.22 (d, J = 6.3 Hz, 3H).

^{13}C NMR (151 MHz, DMSO) δ 166.92 (s), 165.65 (s), 162.64 (s), 133.26 (s), 129.72 (s), 129.13 (s), 128.71 (s), 65.76 (s), 61.34 (s), 34.48 (s), 19.91 (s).

IR (film) cm^{-1}: 2949, 1717, 1638

3-Fluorobutyl benzoate



Colorless liquid

HRMS (ESI) calcd. For [M+Na+] 219.0792, found: 219.0791.

^{1}H NMR (600 MHz, CDCl3) δ 8.06 – 8.01 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 4.97 – 4.79 (m, 1H), 4.52 – 4.37 (m, 2H), 2.15 – 1.94 (m, 2H), 1.41 (dd, J = 23.9, 6.2 Hz, 3H).

^{19}F NMR (565 MHz, CDCl3) δ -175.29 – -175.64 (m).

^{13}C NMR (151 MHz, CDCl3) δ 166.55 (s), 133.07 (s), 130.37 (s), 129.68 (s), 128.48 (s), 87.94 (d, J = 165.7 Hz), 61.23 (d, J = 5.4 Hz), 36.24 (d, J = 21.1 Hz), 21.19 (d, J = 22.5 Hz).

IR (film) cm–1: 2980, 2935, 1716, 1452, 1384, 1269, 1109